# Critical Review of a Proposed List of Toxic Substances to Biomonitor in Michigan Residents

(A Science Report to Governor Jennifer M. Granholm)

Prepared by
Michigan Environmental Science Board
Biomonitoring Investigation Panel

MICHIGAN ENVIRONMENTAL SCIENCE BOARD CONSTITUTION HALL, 5TH FLOOR SOUTH 525 WEST ALLEGAN STREET P.O. BOX 30680 LANSING, MICHIGAN 48909-8180

**July 2003** 

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**July 2003** 



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#### **PREFACE**

#### Michigan Environmental Science Board

The Michigan Environmental Science Board (MESB) was created by the Governor of Michigan by Executive Order 1992-19 on August 6, 1992. The MESB is charged with advising the Governor, the Natural Resources Commission, the Michigan Department of Natural Resources and other state agencies, as directed by the Governor, on matters affecting the protection and management of Michigan's environment and natural resources. The MESB consists of nine members and an executive director, appointed by the Governor, who have expertise in one or more of the following areas: engineering, ecological sciences, economics, chemistry, physics, biological sciences, human medicine, statistics, risk assessment, geology, and other disciplines as necessary. Upon the request of the Governor to review a particular issue, a panel, consisting of MESB members with relevant expertise, is convened to evaluate and provide recommendations on the issue. The MESB is neither a state policy body nor an advocate for or against any particular environmental or public health concern.

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# Critical Review of a Proposed List of Toxic Substances to Biomonitor in Michigan Residents

#### **Major Findings and Conclusions**

The term, biomonitoring, refers to the assessment of exposures to toxic substances in humans by the laboratory measurement of these substances in specimens from human blood, urine, and saliva. Biomonitoring measurements assess the concentration of the toxic substances in humans and can be used to assess the exposure of a single individual or by aggregating data of a population to toxic substances. In recent years, United States (U.S.) health and environmental agencies have been moving towards the increased use of biomonitoring measures in order to better understand the relationship between exposure to environmental pollutants and human health. In May 2001, the U.S. Department of Health and Human Services' Centers for Disease Control and Prevention (CDC) announced the availability of a grant program to promote the planning for the development, implementation, and expansion of state-based biomonitoring programs. The Michigan Department of Community Health (MDCH) applied for and was awarded in October 2001, a two-year grant from the CDC to draft a plan to biomonitor human samples from Michigan residents for toxic substances that are found in the environment and that cause or have the potential to cause adverse human health effects. As part of the plan, the MDCH developed the draft report entitled, Report on the Selection of Priority Chemicals to Biomonitor in Michigan Residents (Draft Report), which lists toxic substances considered to be a priority for biomonitoring in Michigan residents or subpopulations of Michigan residents.

On March 20, 2003, Governor Jennifer M. Granholm requested the Michigan Environmental Science Board (MESB) to review the MDCH Draft Report to evaluate the scientific validity of the rationale for inclusion of each of the toxic substances and to determine whether the known human health risk and pervasiveness of these substances warrant biomonitoring to establish background levels for Michigan residents and/or for identified population subsets at increased risk. On April 11, 2003, a Biomonitoring Investigation Panel (Panel), composed of two MESB members and five guest scientists, was formed to review the Draft Report. Major findings and conclusions of the MESB are summarized below.

- As currently written, the Draft Report does not provide a credible source of rationales for including or excluding many of the identified toxic substances for biomonitoring. In addition, most of the discussions presented are lacking in rigor, clarity, and coherence. The Draft Report would benefit greatly from a much more thorough proofreading.
- ♦ The Draft Report mixes occupational and environmental exposures in its toxic substances' narratives. For example, biomonitoring of workers with the potential for high exposures to a given substance is reasonable given that most substances can become toxic at high enough doses. However, using this information as the basis for biomonitoring of a population who are exposed to much lower environmental levels of the same substance is questionable without some discussion outlining the rationale. In addition, many of the references cited in the Draft Report regarding adverse health effects of the substances do not represent a balanced or rigorous synthesis of the current scientific literature. In many instances, the citations are to single articles that report findings of questionable validity, findings that need confirmation before they should be regarded as demonstrating adverse health effects, and findings for which there is substantial evidence that the health effect is implausible at the body burdens likely to be encountered in the general population. The Draft Report narratives should be reworked to clearly differentiate between occupational and environmental exposures and the adverse human health impacts associated with each.
- ♦ One of the charges to the MESB was to evaluate whether the known human health risk and pervasiveness of the identified substances warrant biomonitoring to establish background levels for identified population subsets of Michigan residents at increased risk. Of the toxic substances proposed by the MDCH, several would be important to biomonitor because Michigan has subpopulations that are believed to have high body burdens for several of these substances. However, the MESB's evaluation of this issue was problematic because few target populations are identified or discussed in the Draft

Report's toxic substance narratives. The need to identify known at-risk population subsets of Michigan residents is important because, just as the National Health and Nutrition Examination Survey (NHANES) relies on a stratified sampling approach with its biomonitoring program, the Michigan program will need to ensure that adequate numbers of samples are collected from the high exposure subpopulations and that the bulk of the time and effort is not spent on collecting samples from the general population that is already being characterized by the NHANES and other biomonitoring projects. The Draft Report could be improved considerably with more in depth discussions regarding who the target populations are and how stratified sampling will ensure that the sample sizes are adequate in the populations of greatest interest.

Assuming that the Draft Report is revised to address the various concerns outlined in this report, the MESB Panel recommends that of the substances proposed for biomonitoring in the general population, methylmercury and lead would be the best candidates. Substances that would be best biomonitored in identified subpopulations would be polychlorinated biphenyls, polybrominated biphenyls, dioxins and furans, and organophosphate pesticides. Substances that should be watched and considered for biomonitoring in the future or possibly considered for pilot investigations to identify current body burdens would be perflurooctanoic sulfate, perflurooctanoic acid, phthalates, and polybrominated diphenyl ethers. The MESB Panel does not consider the information presented in the Draft Report concerning cadmium, manganese, benzene, or dichlorodiphenyltrichloroethane/dichlorodiphenyldichloroethane compelling enough to warrant biomonitoring at this time. Finally, the remaining substance, arsenic, would be a better candidate for drinking water monitoring rather than biomonitoring.

Critical Review of a Proposed List of Toxic

Substances to Biomonitor in Michigan Residents

(A Science Report to Governor Jennifer M. Granholm)



#### Introduction

The term, biomonitoring, refers to the assessment of exposures to toxic substances in humans by the laboratory measurement of these substances in specimens from human blood, urine, and saliva (CDC, 2001a). Biomonitoring measurements assess the concentration of the toxic substances in humans and can be used to assess the exposure of a single individual or by aggregating data of a population to toxic substances. Specific uses of biomonitoring measurements include:

- 1. To measure the prevalence of elevated levels of toxic substances in a population group;
- 2. To determine levels of exposure in population groups who may be at increased risk of exposure;
- 3. To provide levels of human exposure in studies examining the relationship between exposure to a toxic substance and adverse health effects;
- 4. To determine whether levels of toxic substances are higher in potentially more vulnerable population groups such as children, the elderly, or women of childbearing age than in the general population;
- 5. To track over time, trends in the levels of exposure of a population group to specific toxic substances; and
- 6. To assess the effectiveness of public health efforts to reduce the exposure of specific populations to toxic substances.

In recent years, United States (U.S.) health and environmental agencies have been moving towards the increased use of biomonitoring measures in order to better understand the relationship between exposure to environmental pollutants and human health. In particular, the U.S. Department of Health and Human Services' Centers for Disease Control and Prevention (CDC) published biomonitoring data on 27 toxic substances present in the blood and urine of a small sample of the U.S. population in 2001 (CDC, 2001b). In 2003, the CDC released new data on blood and urine residue for 116 toxic substances in a larger nationally representative population sample (CDC, 2003). Considerable biomonitoring data have been collected for a variety of toxic substances including metals, cotinine, volatile organic chemicals, organophosphate pesticides, organochlorine pesticides, phthalates, polychlorinated biphenyls, dioxin and dioxin-like compounds, and polycyclic aromatic hydrocarbons. Additional data are needed in order to determine whether or not the levels of these substances are increasing or decreasing in the U.S. population.

In May 2001, the CDC announced the availability of a grant program to promote the planning for the development, implementation, and expansion of state-based

biomonitoring programs (CDC, 2001a). The Michigan Department of Community Health (MDCH) applied for and was awarded in October 2001, a two-year grant from the CDC to draft a plan to biomonitor human samples from Michigan residents for toxic substances that are found in the environment and that cause or have the potential to cause adverse human health effects. As part of the plan, the MDCH (2003) developed the draft report entitled, *Report on the Selection of Priority Chemicals to Biomonitor in Michigan Residents* (Draft Report), which lists toxic substances considered to be a priority for biomonitoring in Michigan residents or subpopulations of Michigan residents. A copy of the Draft Report is available at http://www.michigan.gov/mesb.

# **Charge to the Michigan Environmental Science Board**

On March 20, 2003, Governor Jennifer M. Granholm requested the Michigan Environmental Science Board (MESB) to review the Draft Report to evaluate the scientific validity of the rationale for inclusion of each of the toxic substances and to determine whether the known human health risk and pervasiveness of these substances warrant biomonitoring to establish background levels for Michigan residents and/or for identified population subsets at increased risk (Granholm, 2003; see Appendix 1). Initially, the MESB also was requested to rank the list of identified substances in the Draft Report, however, based on subsequent discussions with the MDCH, it was determined that the MESB would not need to complete this second task since the toxic substances were already ranked in the Draft Report (Harrison, 2003; see Appendix 2).

On April 11, 2003, a Biomonitoring Investigation Panel (Panel), composed of two MESB members and five guest scientists, was formed. A copy of the Draft Report to be reviewed was provided to the MESB by the MDCH on April 24, 2003. Due to the need to provide comments as soon as possible, no meetings were held by the MESB Panel. Instead, the investigation consisted of an independent review of the MDCH Draft Report by the Panel members.

# Michigan Environmental Science Board Critique

#### **General Comments**

The MDCH Draft Report identifies and discusses 15 toxic substances it considered as possible subjects for biomonitoring (Table 1). The process used by the MDCH to compile its list of toxic substances involved a series of interviews and stakeholder meetings with a wide variety of special interest groups, academies, clinical laboratories, epidemiological, toxicological, and medical professionals within and outside of state government. The criteria used to select the final list of proposed toxic substances to biomonitor were arrived at through discussions with two stakeholder groups and included an evaluation of the 15 toxic substances and a ranking of the (1) known or potential adverse health effect, (2) probability of human exposure, and (3) seriousness of health effect for each substance.

Table 1. List of toxic substances proposed to be biomonitored in Michigan residents.

Methylmercury
Lead
Arsenic
Cadmium
Manganese
Polychlorinated Biphenyls
Polybrominated Biphenyls
Dioxins and Furans

Organochlorine Pesticides
(Dichlorodiphenyltrichloroethane)
(Dichlorodiphenyldichloroethane)
Organophosphate Pesticides
Benzene
Perflurooctanoic Sulfate
Perflurooctanoic Acid
Phthalates
Polybrominated Diphenyl Ethers

For each toxic substance identified, a narrative, comprised of a general background statement and a literature review discussing the probability of exposure, health effects, and severity of effects for the toxic substance, is presented in the Draft Report. With the exception of three substances, each narrative is followed by a bulleted list of reasons why the substance should be biomonitored in Michigan and a list of references that are cited in the narrative.

In general, the Panel encountered several difficulties in reviewing the Draft Report due to problems with its composition, thoroughness, and accuracy. Accuracy issues will be addressed under *Specific Comments* later in this report.

Contributing to the composition problems was the Draft Report's general unpolished state. For example, in the Draft Report's narrative for *Methylmercury* (Pages 3 – 5), there are typographic errors (e.g., 2996 for 1996; et a. for et al., and *methylcercury* for *methylmercury*) and inconsistent reference citations between the text and list of references (e.g., *Clarkson 1997* and *Frustacie et al 1997* are cited in the text but *Clarkson 1975* and *Frustacie et al 1999*, respectively, are found in the list of references). Also, not all listed references are cited in the text (e.g., *Airey, 1983a* and *Airey, 1983b*) and not all text-cited references are in the list of references at the end of the narrative (e.g., *Bakir et al, 1973*). Similar problems were encountered for most of the other toxic substance narratives presented in the Draft Report. Finally, throughout the Draft Report the use of such terms as *high* and *low* are consistently employed without definition or reference to any numerical values, resulting in many meaningless comparisons. Overall, the Draft Report would benefit greatly from a more thorough proofreading, which would have caught the above type of problems.

In terms of thoroughness, there is little discussion in the Draft Report regarding health impacts to Michigan residents for many of the toxic substance narratives (e.g., *Cadmium*, *Manganese*, and *Benzene* narratives), and in those narratives that do address health impacts, the discussion provided often is too general in nature, limiting the reviewer's ability to assess the current state of knowledge of possible exposure effects and, therefore, the need for biomonitoring in people who reside in the state.

Related to the above concern, the Draft Report does not project, based on a review of available literature, a population burden for most of the listed substances. Knowledge of population burden is particularly important since each of the listed substances represents a different and unique exposure profile when considered for the population of the entire state. For those substances where population burden is discussed, the Draft Report alludes only to certain occupational exposures and geographically specific exposures. For those substances where information is available, a discussion should be devoted to: (1) the sub-populations that should be considered principally at risk for individual exposures, (2) the different gradations of risk, and (3) the severity of exposure for each of the substances, applied to specific populations at risk. In general, each of the Draft Report toxic substance narratives would benefit greatly from a more thorough literature search and a more robust discussion that focuses on the most recent and pertinent literature.

Finally, very little is mentioned in the toxic substances narratives about temporal trends. Each of the substances listed is associated with changing environmental concentrations over time. This is more relevant to some exposures than others. For example, point source exposure to polybrominated biphenyls in Michigan (Pages 18-20) occurred over 25 years ago and residual exposures today are minimal. Also, specific attention should be paid to the decreasing amounts of dichlorodiphenyltrichloroethane (Pages 25-28) in the environment since this pesticide was banned decades ago.

## **Specific Comments**

#### Criteria for Chemical Selection

As previously indicated, the MESB Panel recognizes that the process and criteria used in the Draft Report to select and rank substances were subjective. However, the selected process still would have been strengthened with a more thorough description. For example, it is unclear from the description in the Draft Report what the basis was for: (1) Assigning a health effects range of 0 - 5 and the sub-rankings of range 4 - 5 with 0 being assigned if the substance did not fall into the sub-ranking categories; (2) Assigning a probability of exposure range of 0 - 3.5, with subcategories of 3.5 and 3.0 and none of the above assigned 0; (3) Assigning ranks for seriousness of health effect 0 - 2.5; and (4) Adding ranks for effects that occur early in life and multigenerational to get a combined score of 4.5.

In addition, it is unclear, without further description in the text, how the Draft Report's ranking system relates to its Appendix entitled, *Priority Chemicals to Biomonitor* (Page 50) since for eight of the substances listed in the Appendix (*Mercury, Lead, Cadmium, Dioxins and Furans, Polychlorinated Biphenyls, Polybrominated Biphenyls, Brominated Compounds, and Organophosphate Pesticides*), the *Exposure Probability* value equals 5.0 and, therefore, exceeds the *Probability of Exposure* range of 0 to 3.5 established in the *Criteria for Chemical Selection* text (Page 2).

Finally and of greater concern to the Panel, is the fact that the selection criteria used in the Draft Report appear to disregard dose-response (i.e., it can add together effects at high doses with exposures at low doses). Using this particular type ranking system, just about any substance that is labeled as a carcinogen (as well as a number that are not) and is found in the environment could be considered a priority substance in need of biomonitoring.

## Methylmercury

The *Methylmercury* narrative does not clearly differentiate a number of aspects of mercury exposure and toxicity that are critical to evaluating its importance. These include the differences between: (1) inorganic and organic mercury, (2) effects in adults and children, and (3) fish caught in inland lakes versus Great Lakes versus oceans. Also, it is surprising in light of the fact that Michigan in 1970 was the first state in the nation to issue fish consumption advisories based on mercury (Hesse, 1997), that a discussion on the state's annual fish consumption advisory program and the various sensitive sub-populations of Michigan residents it is designed to protect was not provided in the narrative.

<u>Page 3, Background.</u> The chemical forms of methylmercury should be specified, (e.g.,  $CH_3Hg^{\dagger}$ ,  $CH_3HgCI$ ,  $CH_3HgCH_3$ , etc.). Also, the term, *aquatic organisms*, needs to be defined since this could include bacteria as well as higher organisms.

<u>Page 3, Probability of Exposure.</u> The second paragraph of this section states: "Methylmercury can accumulate at greater rates than that excreted." Research has shown that methylmercury pharmacokinetics fit a single-compartment model with continuous input and first-order elimination (Carrier et al., 2001; Young, Wosilait and Luecke, 2001; Smith and Farris, 1996; Tuey, 1980). Consequently, accumulation will occur with the plateau level being determined by the relative magnitudes of the input rate and the first-order elimination rate constant.

The referenced Hightower and Moore (2003) study in the third paragraph of this section appears to be misinterpreted. The narrative states: "These results suggest that high fish consumption may pose a risk for exposure to methylmercury levels above the current standard and that these levels may be associated with neurological problems;" however, the Hightower and Moore (2003) study states: "Cause and effect regarding symptoms was not fully addressed in this study." It then discusses all of the data that were not collected and which would be needed to establish cause and effect. Finally, the Hightower and Moore (2003) study was performed to determine mercury levels, not mercury toxicity. Also, there appears to be confusion regarding RfDs (Reference Doses) and blood levels. While there is a blood level of mercury that correlates with the RfD, these are not the same thing - the former is the concentration in blood and the latter is an estimate of the acceptable daily intake.

Finally, it is important to note that associations are not established adverse effects as implied in the fourth paragraph. Reference also is made to *effects* of mercury on

various physiological parameters. However, it is not clear in the narrative that the effects were adverse effects.

<u>Page 4, Why Methylmercury should be biomonitored in Michigan.</u> Methylmercury would be better referred to as a *neurotoxicant* rather than a *neurotoxin*. Also, additional evidence regarding the special sensitivity of the developing fetus would be useful to the narrative.

#### Lead

<u>Page 6, Background.</u> There is a misunderstanding of the relationship of the National Priority List (NPL) of hazardous waste sites and federal Superfund sites. The NPL list is a result of the implementation of the federal Superfund program; consequently, discussing these as if there is a Superfund list and an NPL list is incorrect - they are one and the same.

Page 6, Probability of Exposure. The statement: "Given the widespread distribution of lead in the environment, everyone has a low background level of around 1.66 ug/dL (CDC, 2003)," is misleading. The statement appears to be derived from Table 2 of the CDC (2003) discussion on lead and actually refers to the geometric mean of blood concentrations for the U.S. population aged one year and older. Also, the unit ug/dl is incorrect in the above referenced sentence and throughout the narrative. The actual unit should be ug/dl.

BLL is incorrectly defined in the second paragraph as Blood Lead rather than Blood Lead Level.

<u>Page 6, Health Effects.</u> The phrase, *reproductive problems*, is mentioned twice in two separate locations of the paragraph, as is its referenced text-citation (*reviewed in Juberg, 2000*), which is redundant and confusing. In addition to the adverse effects mentioned in the paragraph, the narrative should mention that the nervous system effects in adults are primarily in the peripheral nervous system at relatively high levels of exposure.

The reported effects in the second paragraph on IQ (Intelligence Quotient) at blood lead levels as low as 10  $\mu$ g/dl are somewhat controversial (ATSDR, 1999; Pocock, Smith and Baghurst, 1994). Also, the claim that lead causes hematological problems at blood lead levels of 10  $\mu$ g/dl is misleading. While it is established that lead inhibits  $\delta$ -aminolevulinic acid dehydratase at this level, characterizing this as a *hematological problem* is not accurate (ATSDR, 1999). It is unclear if the hematological problems referenced in this paragraph are biomarkers of exposure or actual adverse effects. Finally, *BBL* is incorrectly used for *BLL* in the last sentence.

It is not clear what is meant in the first sentence of the third paragraph by "...very low blood lead levels...." Second, the third sentence is confusing. For example, it is stated: "In a recent study of 240 children enrolled between 5 and 7 months for an

unrelated study (Canfield et al., 2003). BLLs were obtained at 6, 12, 18, 24, 36, 48, and 60 months of age." First of all, the period following Canfield et al, 2003 should be a comma. Second, and more important, it is unclear what study is being cited from Canfield et al. (2003), the recent study or the unrelated study. Finally, the paragraph did not referenced the cautionary statements by Canfield et al. (2003) regarding the investigation's counterintuitive observations that blood lead levels in children below of 10  $\mu$ g/dl have a greater effect on IQ than blood lead levels greater than 10  $\mu$ g/dl. For example, Canfield et al. (2003) states, "As with any observational study, it is not possible to draw causal inferences from these findings. Instead, the plausibility of a causal interpretation must be judged by the consistency of findings from numerous epidemiologic studies and the relevant experimental studies in animals."

The citation for the first sentence in the fourth paragraph is given as *Kent, 2001*; however, no such reference exists in the list at the end of the narrative; unless *Kent, 2001* is suppose to refer to *Kent County Health Department, Unpublished 2001 Datafile*, which does appear in the list of references. This is confusing since the reviewer has no way of knowing if the statistics described in the sentence is referring to Michigan as a whole or just Kent County, Michigan. It also is unclear how the \$1.4 billion figure was derived and the source for that statement. Finally, the inclusion of the economic statistics in the otherwise health effects discussion is not necessary since economics is not one of the selection criteria concerns defined by the MDCH for biomonitoring and is not used in any of the other toxic substance narratives in the Draft Report.

<u>Page 7, Why Lead should be biomonitored in Michigan.</u> This is the only area where statistics discussing the city of Detroit are referenced in the entire narrative. It would have been more logical to include these in the *Health Effects* section along with the Michigan statistics. Similarly, it is puzzling why the Michigan statistics that were summarized in the *Health Effects* section were not referenced in this section as an additional reason for biomonitoring since it certainly would have added to the case for the need to biomonitor.

#### Arsenic

<u>Page 8, Background.</u> The use of the term, *Oxidation state*, is more appropriate than the term, *valency state*, in the second sentence of the paragraph. This is an example of the inconsistent treatment in the Draft Report for the different metals. For example, oxidation states are provided in the *Arsenic* narrative, but not in the *Methylmercury*, *Lead*, *Cadmium*, or *Manganese* narratives. In particular, manganese has a relatively large number of oxidation states and, consequently, a relatively complex chemistry and toxicology.

<u>Page 9, Health Effects, General.</u> There is no discussion in this section regarding the carcinogenicity of arsenic despite the fact that considerable information is available on this topic (ATSDR, 2000). Also, distinctions in exposure and toxicity among various arsenic compounds that are referenced in this section are unclear.

<u>Page 9, Health Effects.</u> An inconsistent nomenclature is used to designate arsenic (As) oxidation states. In this section, As(III) is used, whereas earlier (in the <u>Background</u> section), +3 was mentioned. In the second sentence, it is stated: "As(III) is 25 - 60 times more toxic than As(V)," but no reference for this is given. It also is stated: "[As(III)] ... is several hundred times as toxic as organic arsenicals," but this clearly depends on the particular organic arsenic compound and its oxidation state in the organic compound.

<u>Page 9, Probability of Exposure.</u> The maximum concentration level (MCL) referenced for arsenic in the third paragraph of this section is based on a 1982 U.S. Environmental Protection Agency (USEPA, 1982) publication and does not reflect recent action to lower the MCL to 10 mg/l (USEPA, 2001). Also, the lengthy description of the endemic Blackfoot disease in Taiwan is irrelevant to the discussion.

<u>Page 9, Why Arsenic should be biomonitored in Michigan.</u> From the narrative, it is unclear what will be biomonitored and what the concentrations will be compared to. It is questionable how useful biomonitoring of arsenic would be unless adverse human effect concentrations are known. A more productive plan would be to monitor drinking water; which, however, is not the same as biomonitoring.

#### Cadmium

<u>Page 11, Background.</u> Another important use of cadmium that should be mentioned is in the electroplating of metals.

<u>Page 11, Probability of Exposure.</u> The case for cadmium would be more compelling in the second paragraph if the concentrations found in the National Health and Nutrition Examination Survey (NHANES) 1999 - 2000 (NCHS, 2003) were toxicologically relevant. Little is presented in this section to suggest that the general Michigan population might be exposed to cadmium in any significant concentrations.

<u>Page 11, Health Effects.</u> Without a numerical value or reference point, it is unclear what is meant by *at high exposure levels* in this paragraph. Also, it would be useful to mention routes of exposure in the discussion of health effects. For example, it is implied in the discussion regarding pulmonary effects that the route of exposure is inhalation of metal fume or dust, but this is not stated. The distinctions between environmental and occupational exposures as well as between ingestion and inhalation exposures are not clear in this paragraph. Finally, there is no convincing evidence provided in the discussion that environmental exposure levels are related to any observed adverse human health effects.

<u>Page 12, Seriousness of the Health Effects.</u> The source document cited for the International Agency for Research on Cancer (IARC) in this section is *IARC, 1987*; however, the only *IARC, 1987* appearing in the list of references for this narrative is, *IARC. Lead and lead compounds. IARC Monogr Eval Carcinog Risk Hum 1987;23:325-415*, which is an inaccurate reference. There have been three reports produced by the

IARC entitled, *Cadmium and Certain Cadmium Compounds* (IARC, 1993, IARC 1982, and IARC, 1976). It appears that the MDCH used information from the *IARC*, 1982 publication. If this is the case, the newer IARC (1993) report should be used since it would have the most relevant information regarding carcinogenicity.

<u>Page 12, Why Cadmium should be biomonitored in Michigan.</u> While considerable information is available regarding occupational exposure to cadmium and adverse health effect, there is no convincing evidence provided in the narrative that exposure to environmental levels of cadmium are related to adverse human health effects. Consequently, without additional justification, there is no reason to believe that the Michigan population might be exposed to cadmium in significant concentrations.

## Manganese

<u>Page 13, Background.</u> There is no mention of the rich oxidation state chemistry of this metal in this section.

<u>Page 13, Probability of Exposure.</u> Little evidence is provided to suggest adverse human health effects from environmental (versus occupational) exposure in Michigan. Also, no evidence is presented in this section to support the Draft Report's statement: "MET [methylcyclopentadienyl manganese tricarbonyl] use in Michigan is increasing."

<u>Page 13, Health Effects.</u> This section only discusses health effects resulting from occupational exposure and does not address any health effects from environmental exposure to the general population.

<u>Page 14, Why Manganese should be biomonitored in Michigan.</u> Overall, there is no compelling argument presented in the narrative to suggest a need for biomonitoring of manganese in Michigan.

# Polychlorinated Biphenyls

<u>Page 15, Background.</u> There are no references cited to support any of the information provided in the second paragraph. Without the sources for the statements, it is not possible to verify the validity of the statements.

<u>Page 15, Probability of Exposure.</u> The use of a text-cited newspaper article (Webber, 2000) to support a rationale in this section is inappropriate. Exposure estimates ignore differences between inland lakes and Great Lakes, and ignores more recent information contained in the annual *Michigan Fish Advisory* on compliance. The text citation, *Canada, 1991*, is not listed in the references at the end of the narrative. The term, *DDE*, is undefined in this section. In general, the Great Lakes data are based on dated publications. More recent data on polychlorinated biphenyls (PCBs) in Great Lakes fish are presented in the annual *Michigan Fish Advisory* and, therefore, should be readily available to the MDCH.

<u>Page 15, Health Effects.</u> The use of the phrase, *inhalation, or in the air*, in the first sentence is redundant. The phrases, *exposed directly to high levels* (First sentence, First paragraph), *only a few chlorine atoms* (Second paragraph, First sentence), and *more highly chlorinated PCBs* (Second paragraph, Fourth sentence), are not defined in this section. It would be useful if numerical values could be used to describe or provide a reference as to what is meant by *high* and *few*, and an example provided of what would be considered a *more highly chlorinated PCB*. Also, the points made in the last two sentences in the first paragraph appear to be contradictory. For example, is it the fact that exposure to more highly chlorinated PCBs is altering normal estrogen levels, or is the process of biotransformation of the more highly chlorinated PCBs to lower chlorinated PCBs that is altering the levels? Finally, the citation of the Internet address, *http://www.clearwater.org/news/*, in the narrative is inappropriate.

<u>Page 16, Seriousness of Health Effects.</u> The reference to *IARC, 1978* in the second paragraph is outdated. Many of the studies referenced in the second paragraph of this section were poorly designed with small numbers, poor matching of controls, and many unaccounted for confounders. The text-cited reference, *Taylor et al.*, does not have a date associated with it and also does not show up in the list of references at the end of the narrative.

<u>Page 16, Why PCBs should be biomonitored in Michigan.</u> The two bulleted statements in this section are highly generalized. It would have been helpful to have provided a statement in the bulleted list, based on the previous PCB narrative that would specifically support the need for biomonitoring either in the general or a particular subpopulation of Michigan residents.

#### Polybrominated Biphenyls

Page 18, Probability of Exposure. Although this section provides a reasonable discussion on historic exposure to PBBs, no discussion is provided regarding the likelihood or unlikelihood of current exposures to PBBs that could help to put the Michigan PBB problem into perspective. For example, according to the ATSDR (2002a), "PBBs are no longer produced or used in the United States. Thus, the general population exposure to PBBs will only be from historical releases. For people residing in the lower peninsula of Michigan, especially in the immediate vicinity of the PBB contaminated areas of this region, exposure to PBBs may still be occurring today. However, environmental levels have decreased since the 1970s and current exposure, if any, will be at low levels. For other regions of the United States, the levels of exposure will either be very low or none."

<u>Page 19, Seriousness of Health Effect.</u> The discussion of cancer in the second paragraph could have been improved by further elaboration and by consulting the discussion contained the ATSDR (2002a) draft review of the topic. For example, it would have been useful for the Draft Report to discuss its referenced Hogue *et al.* (1998) study, which states that it "... found a significantly increased risk [of cancer] with the highest serum levels ... and ... significant risks of cancer for the digestive system

and for lymphoma although the number of cases for any cancer was low," and the ATSDR (2002a) review, which states: "Suggestive relationships between increasing serum levels of PBBs and risks of breast cancer, digestive system cancer, and lymphoma (not otherwise specified) were found in case-control studies of Michigan PBB registry enrollees who were followed for approximately 20 years." Finally, the word, enrolment, in this paragraph is misspelled.

<u>Page 19, Why PBBs should be biomonitored in Michigan.</u> From the narrative, a case can be made for biomonitoring of the exposed population and their progeny but not for the general population of Michigan.

#### **Dioxins and Furans**

<u>Page 20, Background.</u> Some indication of the type of toxicity that forms the basis for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) being as toxic as indicated in this section would be helpful.

<u>Page 21, Probability of Exposure.</u> In the first paragraph, the cancer potency is confused with the acceptable daily intake. Also, the discussion suggests that a large number of cancers are attributable to dioxin-like compounds, which is not supported scientifically. If the risk of cancer is as high as indicated from the discussion of levels, food, and potency, then it should be possible to provide epidemiological studies of general population exposure to dioxin demonstrating that dioxin is causing cancer. This has not been provided; all of the epidemiological evidence provided relates to high dose exposure.

It would be useful to provide in the second paragraph of this section a discussion on how serum levels relate to levels producing toxicity. There is confusion in this section between TCDD levels and toxic equivalency quotients. Also, the discussion omits that the main route of exposure is thought to be ingestion of food so exposure is likely even in non-industrial areas. Sources of information on the relative importance of food exposure that should be consulted include the ATSDR (1998) and the USEPA (2000) draft reassessment document on dioxin.

Finally, the reference to NHANE III data collected in 1999 – 2000 is incorrect in the fourth paragraph of this section. The data actually were collected in 1988 – 1994.

Page 23, Why TCDD should be biomonitored in Michigan. Given that TCDD exposure is generally decreasing in the U.S. and the only conclusive human health effects data currently are from studies involving occupationally, Agent Orange, or industrial accident exposed populations to significant amount of TCDD (USEPA, 2000), there is no compelling rationale presented in the narrative to biomonitor TCDD and related dioxins in the general population of Michigan. However, biomonitoring in heavily contaminated regions of Michigan, for instance in the Saginaw Bay watershed (Taylor, 2002), and comparing that to another geographic area with a less exposed population may be justifiable and should be considered.

## Organochlorine Pesticides

<u>Page 25, Background.</u> The term, *DDE*, is not defined.

Page 25, Potential for Exposure. The statement: "... potential for human exposure is very high," does not define very high. The statement: "Farmers, as a group, may be particularly at risk," does not seem realistic considering that uses of most of the organochlorine pesticides have been banned for many years. The reference to phenoxy herbicides is not appropriate in this section since phenoxy herbicides are not organochlorine pesticides. Also, the statement: "Exposure to endocrine-disrupting pesticides, particularly to DDT and phenoxy herbicides, is suspected of involvement in some of these hormonal cancers," is without merit since dichlorodiphenyltrichloroethane has been banned for decades and the phenoxy herbicides do not bioaccumulate (Howard, 1991). There are no sources referenced for any of the statements in this section. Without the sources for the statements, it is not possible to verify the validity of the statements.

<u>Page 25, References.</u> Three references are listed at the end of the *Organochlorine Pesticides* narrative. Of these, two are not cited in the narrative (*Buranathevedh and Roy, 2002* and *Charlier, 2002*) and the third is misspelled (*Rind* in the text and *Rhind* in the list of references).

<u>Dichlorodiphenyltrichloroethane</u> and <u>Dichlorodiphenyldichloroethane</u>. The exposure data (e.g., Smith, 1991; Hunter *et al.,* 1997) used in the narrative for dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethane (DDE) are dated. More recent data discussions on DDT and DDE are available (CDC, 2003; ATSDR, 2002b). Also, in the absence of any discussion in the narrative to relate ecotoxicity effects to human health and given that ecotoxicity was not one of the toxic substances selection criteria, the ecotoxicity discussion in this section is out of place.

The discussion in the *Seriousness of Health Effects* section ignores evidence indicating a very weak relationship between environmental exposure to organochlorine pesticides and cancers given that: (1) there is current debate regarding organochlorine pesticides being threshold carcinogens (i.e., high dose animal studies cannot be extrapolated simply to low dose human exposures) and (2) despite their widespread use and persistence in the environment, there is no clear epidemiological evidence supporting the relationship between DDT and cancer in humans (ATSDR, 2002b).

Based on the information presented in both the *Organochlorine Pesticides* and *DDT/DDE* narratives, the Draft Report provides no compelling rationale for the need to biomonitor organochlorine pesticides in Michigan. The Draft Report's statement: "Due to their widespread use and persistence in the environment, many Michigan residents are likely to have measurable levels [of organochlorine pesticides], especially of *DDT/DDE*," is based on a use that for many of the organochlorine pesticides are decades old. Also, the term, measurable, in the above sentence is a relative term given

analytical technology and does not necessarily equate to levels that would adversely impact health. In addition, and for at least DDT, body burdens have continued to decrease (albeit slowly) over time (ATSDR, 2002b). Consequently, the potential for either existing body burdens adversely affecting health or future exposure is greatly minimized. One weak rationale for biomonitoring of these substances not discussed in the Draft Report is provided by the CDC (2003) and refers to a concern that new exposure may be coming from imported food from countries that still use organochlorine pesticides such as DDT (CDC, 2003). In order to consider this though, there would need to be, at the very least some statistics provided in the Draft Report to document a sizable importation of such contaminated foods into Michigan.

# Organophosphate Pesticides

<u>Page 28, Background.</u> The narrative needs to be specific with its enzyme terminology. The target enzyme for the organophosphates is acetylcholinesterase (AChE). Also, the acute toxic effects listed only occur with high-level exposures.

<u>Page 29, Probability of Exposure.</u> It is not clear what the relevance is for including a discussion of the overlap of metabolites. Also, there is no date associated with the text-cited reference, *Michigan Dept. Ag*.

<u>Page 29, Health Effects.</u> It is not clear why a discussion of acute effects is included in this section since biomonitoring is not appropriate for acute effects. It is incorrect to link the signs and symptoms listed with inhibition of serum cholinesterase (butyrylcholinesterase - BChE). The effects indicated would be related to central nervous system/peripheral nervous system inhibition of AChE, not BChE. BChE inhibition is a biomarker of exposure and not an indication of toxicity. Reference to the Internet web site (*Organophosphate, 2003*) in this section not appropriate unless it is peer reviewed. Organophosphate-induced delayed neuropathy cannot occur from exposures to organophosphate pesticides that are currently registered for use in the U.S. except for certain organophosphate pesticides after medically assisted survival of supralethal doses (e.g., from suicide attempts). Finally, it would be useful if the term, *low levels*, which is used throughout this section, was defined.

<u>Page 30, Seriousness of Health Effects.</u> It is essential to indicate actual doses used in the studies that were cited in this section. In most cases, toxic effects do not occur at environmentally relevant doses.

Why Organophosphate Pesticides should be biomonitored in Michigan. The organophosphate pesticides are rapidly metabolized and excreted in the urine. To measure these in the general population would result in a large number of non-detects. Some monitoring in the farmer and farm-worker population may be justified but may be duplicative of the NHANES projects.

<u>Page 30, References.</u> Two references in the listing at the end of the narrative do not appear in the narrative (*Curl et. al., 2002* and *Rodnitzky, 1975*).

#### Benzene

<u>Page 31. Background.</u> Benzene is not a polycyclic hydrocarbon. The U.S. domestic benzene importation amount (4,794,533,678 L) does not seem correct, especially if the L means *liter*.

Page 32, Seriousness of Health Effects. It is unclear what the term, substantially lower means in the sentence, "A 2001 review on benzene exposure and lymphohematopoietic malignancies in humans also provided further evidence for hematopoietic cancer risks at benzene levels substantially lower than had previously been established." Finally, there is no evidence provided in the section that non-occupational exposures result in adverse human health impacts.

<u>Page 32, Why Benzene should be biomonitored in Michigan.</u> There does not exist in the narrative any support for the statement: "... benzene levels in the environment are increasing." Finally, while there does not appear to be much evidence of adverse effects from benzene exposure in non-occupationally exposed individuals, it still may be valuable to collect data from the general population, as exposures are likely frequent.

## **Emerging Chemicals of Concern**

The Introduction section clearly indicates that the toxic substances to be discussed, Perfluoctanic Sulfate, Perfluroctanoic Acid, Phthalates and Polybrominated Diphenyl Ethers, are not proposed for biomonitoring based on the same selection criteria outlined in the Draft Report for the other identified substances. For instance, little direct evidence exists regarding adverse human health effects for any of the identified Emerging Chemicals of Concern and greater weight is given to accumulating evidence regarding impact to the environment and animals from these substances. Still, each of the following narratives could have been improved with a discussion and a presentation of pertinent data on exposure in the general population to help in characterizing possible risks.

Perfluroctanoic Sulfate and Perfluroctanoic Acid. Although it is indicated in the narrative that, "... perfluroctanoic sulfate [PFOS]-related compounds have been found in surface waters, sediment downstream of a production facility, wastewater treatment plant effluent, sewage sludge and landfill leachate at a number of cities in the USA," there is no additional information provided to the reviewer regarding at what concentrations the substances have been found and also no indication that any of the identified locations were even in Michigan. This makes it difficult to evaluate how extensive the prevalence of PFOS is in the Michigan environment. In addition, the evidence presented for the health effects of perfluorinated compounds is weak given the limited number of scattered studies performed and does not provide a data base sufficient to estimate the toxicity of these compounds.

**Phthalates.** The toxicity of phthalates is not well characterized in the narrative. There are different concerns with different phthalate compounds. Consequently, it would have been better if the various compounds were addressed individually and in greater detail rather than grouping them all together under one discussion. Also, there was no source provided for the *Puerto Rican girls*' study referenced in the *Health Effects* section of the narrative. Given the probability of exposure to phthalates, some biomonitoring may be appropriate, however before proceeding, additional characterization of potential risks would be useful. The additional research could assist in identifying the particular phthalate compounds most appropriate for biomonitoring. Finally, the unit of measure used in this narrative (ug/mL) is incorrect. The actual unit should be  $\mu g/mL$ .

<u>Polybrominated Diphenyl Ethers.</u> References need to be provided in the *Background* section of the narrative. Background and toxicological information on polybrominated diphenyl ethers (PBDEs) are readily available in the ATSDR's (2002a) *Draft Toxicological Profile for Polybrominated Biphenyls and Polybrominated Diphenyl Ethers.* Sentences are generally not begun with a number (e.g., 98% of the global production was for the USA).

Based on information presented in the narrative as well as on other information not contained in the narrative (e.g., Norstrom *et al.*, 2002), PBDEs have become prevalent and concentrations of PBDEs have increased in certain Michigan Great Lakes fish and eggs of some fish-eating birds over the last 20 years. Although little information is known about human exposure to PBDEs (ATSDR, 2002a), what is known suggests that the most likely source of exposure to humans would be from consumption of Great Lakes fish. In terms of adverse health effects, with the exception of the few studies referenced in the narrative, little information also is known regarding the substances' effect on human health (ATSDR, 2002a).

In general, while there exists little human exposure or human health effects information for any of the identified *Emerging Chemicals of Concern*, information regarding the ubiquitous nature of these substances in the environment is increasing and biomonitoring of the Michigan population or an identified subpopulation may be useful in the development of a new database for human health effects. This may result in recognition of new environmental contamination that may impact on human health. The rationale for pursuing this could be made much more convincing in the Draft Report by addressing how the Michigan biomonitoring project could appreciably increase the knowledge base for these substances.

#### Conclusions

As currently written, the Draft Report does not provide a credible source of rationales for including or excluding many of the identified toxic substances for biomonitoring. In addition, most of the discussions presented are lacking in rigor, clarity, and coherence. The Draft Report also would benefit greatly from a much more thorough proofreading.

The Draft Report mixes occupational and environmental exposures in its toxic substances' narratives. For example, biomonitoring of workers with the potential for high exposures to a given substance is reasonable given that most substances can become toxic at high enough doses. However, using this information as the basis for biomonitoring of a population who are exposed to much lower environmental levels of the same substance is questionable without some discussion outlining the rationale. In addition, many of the references cited in the Draft Report regarding adverse health effects of the substances do not represent a balanced or rigorous synthesis of the current scientific literature. In many instances, the citations are to single articles that report findings of questionable validity, findings that need confirmation before they should be regarded as demonstrating adverse health effects, and findings for which there is substantial evidence that the health effect is implausible at the body burdens likely to be encountered in the general population. The Draft Report narratives should be reworked to clearly differentiate between occupational and environmental exposures and the adverse human health impacts associated with each.

One of the charges to the MESB was to evaluate whether the known human health risk and pervasiveness of the identified substances warrant biomonitoring to establish background levels for identified population subsets of Michigan residents at increased risk. Of the toxic substances proposed by the MDCH, several would be important to biomonitor because Michigan has subpopulations that are believed to have high body burdens for several of these substances. However, the MESB's evaluation of this issue was problematic because few target populations are identified or discussed in the Draft Report's toxic substance narratives. The need to identify known at-risk population subsets of Michigan residents is important because, just as the NHANES relies on a stratified sampling approach with its biomonitoring program, the Michigan program will need to ensure that adequate numbers of samples are collected from the high exposure subpopulations and that the bulk of the time and effort is not spent on collecting samples from the general population that is already being characterized by the NHANES and other biomonitoring projects. The Draft Report could be improved considerably with more in depth discussions regarding who the target populations are and how stratified sampling will ensure that the sample sizes are adequate in the populations of greatest interest.

Assuming that the Draft Report is revised to address the various concerns outlined in this report, the MESB Panel recommends that of the substances proposed for biomonitoring in the general population, methylmercury and lead would be the best candidates. Substances that would be best biomonitored in identified subpopulations would be PCBs, PBBs, dioxins and furans, and organophosphate pesticides. Substances that should be watched and considered for biomonitoring in the future or possibly considered for pilot investigations to identify current body burdens would be PFOS, PFOA, phthalates, and PBDEs. The MESB Panel does not consider the information presented in the Draft Report concerning cadmium, manganese, benzene, or DDT/DDE compelling enough to warrant biomonitoring at this time. The remaining substance, arsenic, would be a better candidate for drinking water monitoring rather than biomonitoring.

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# Appendix 1

# March 20, 2003 Correspondence to the Michigan Environmental Science Board from Governor Jennifer M. Granholm

(Granholm , J.M. [2003]. Correspondence to Dr. Lawrence Fischer, Michigan Environmental Science Board, March 20, 2003. Office of the Governor, Lansing. 1p.)



#### STATE OF MICHIGAN

#### JENNIFER M. GRANHOLM GOVERNOR

# OFFICE OF THE GOVERNOR LANSING

JOHN D. CHERRY, JR.

March 20, 2003

Lawrence J. Fischer, Ph.D., Chair Michigan Environmental Science Board Constitution Hall, 5th Floor South P.O. Box 30680 Lansing, Michigan 48909-8180

Dear Dr. Fischer:

The Michigan Department of Community Health (MDCH) has received funding from the Centers for Disease Control and Prevention to develop a plan to monitor residents in the state of Michigan for exposure to toxic chemicals. As part of the plan, the MDCH is to develop a priority list of chemicals for biomonitoring and identify the subgroups of Michigan residents who could have increased sensitivity to adverse effects from exposure to these chemicals. The MDCH anticipates that it will have its draft list of priority chemicals and rationale compiled by February 2003.

I am requesting that the Michigan Environmental Science Board (MESB) review and rank the list of chemicals to determine the scientific validity for the following:

- The rationale for inclusion of each chemical.
- Rank chemicals in terms of real or potential health risk.

In addition, I request that the MESB evaluate whether the known human health risk and pervasiveness of these chemicals warrant biomonitoring them to establish background levels for Michigan residents and/or to identify population subsets at increased risk.

I encourage the Board to seek input from outside interests or experts and would appreciate the completion of this evaluation by April 2003.

Thank you for your continuing service to the citizens of Michigan.

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Sincerely

Jennifer M. Granholm

Governor

cc: Ms. Janet D. Olszewski, Director, MDCH

Mr. Keith G. Harrison, Executive Director, MESB





# Appendix 2

# April 18, 2003 Correspondence to the Michigan Department of Community Health from the Michigan Environmental Science Board

(Harrison, K.G. [2003]. Correspondence to Ms. Janet D. Olszewski, Director, Michigan Department of Community Health, April 18, 2003. Michigan Environmental Science Board, Lansing. 1p.)



JENNIFER M. GRANHOLM

#### STATE OF MICHIGAN MICHIGAN ENVIRONMENTAL SCIENCE BOARD LANSING

KEITH G. HARRISON EXECUTIVE DIRECTOR

April 18, 2003

Ms. Janet D. Olszewski, Director Department of Community Health Lewis Cass Building 320 South Walnut Street Lansing, Michigan 48913

Dear Ms. Olszewski:

The purpose of this letter is to clarify Governor Jennifer M. Granholm's March 20, 2003. request to the Michigan Environmental Science Board (MESB) regarding its review of the Department of Community Health's (DCH) report on priority chemicals to biomonitor in Michigan residents. In Governor Granholm's letter, it was requested that the MESB "... rank the list of chemicals," in one instance and "...rank the identified chemicals in terms of real or potential health risk," in another instance. Based on discussions with the principal DCH author of the report to be reviewed by the MESB, Dr. Julie Wirth, the DCH report will have already ranked the chemicals and, therefore, this will not need to be completed by the MESB. The MESB will, however, continue its evaluation of the DCH rationale for inclusion of each of the identified chemicals and determine whether or not the known human health risk and pervasiveness of these chemicals warrant biomonitoring to establish background levels for Michigan residents and/or for identified population subsets at increased risk.

Should you have any questions, please contact me at 517-373-4960.

Sincerely,

Keith G. Harrison, M.A., R.S., Cert. Ecologist

Executive Director

Ms. Jennifer M. Granholm, Governor Dr. Lawrence Fischer, MESB Chair

Dr. Julie Wirth, DCH



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